THE INFLUENCE OF HEREDITY IN THE ETIOLOGY OF TUBERCULOSIS.

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Introduction.

The question as to whether tuberculosis is a hereditary disease is never nowadays discussed.

From the point of view of the public weal it might seem useless to spend time on questions of a secondary interest instead of devoting every effort to the fight against tuberculosis itself. But if we are driven to the most urgent and most practical course, it is nevertheless unwise to forget altogether problems which may momentarily be set aside.

Recent genetical and eugenic work have once more called into notice the problems of heredity in tuberculosis to which a recent analysis of this question brought us.

"In tuberculosis, heredity completes the history of the disease; the modal reactions of the individual in contact with this infection are frequently controlled by predispositions, tendencies and resistances bequeathed by the parents."*

We also put forward the opinion that while in tuberculosis one cannot speak of specific heredity or germinal inheritance, nevertheless we are face to face with transmission through parents attacked by this malady of a particular "*dynamism*," rendering the children more susceptible to the contraction of tubercular or paratubercular troubles.

To verify this conception one should take concrete instances and analyse the records of the descendants of tubercular parents, comparing them with those of healthy individuals, care being taken to work only on homogenous groups sheltered from miscellaneous influences, such as the study which we have endeavoured to carry out.

B.—Method.

In biology, when it is desired to analyse the hereditary constitution of a species, experimental crosses are made of two fixed lines of which the offspring may be carefully observed. Obviously no human matings could give such experiments, as these must necessarily be

*Dr. A. Govaerts—"Heredity in Tuberculosis." Belgian National League against tuberculosis. Meeting of the Principal Committee on April 5th, 1923.

conditioned by other and very different considerations than those which engross geneticists. We must take human descent as we find it.

This circumstance makes the eugenist's work difficult. The number of sources of error is increased, and factors capable of influencing phenomena multiply. The investigator is forced to observe a great number of cases so that these influences may compensate each other. He must also be able to deal with stable and identical groups. as far as possible isolated from other disturbing influences.

In spite of all these precautions, studies of human generations can only result in approximations, unless indeed the conclusions be verified by experimental facts. Finally the notions which we draw from these researches will only bear the stamp of probability; they can only be applied collectively not individually. That is why eugenics is rather a means than an end, an indication for the Officer of Health as to the application of established scientific principles.

The Hygiene Insitution Centre established at Jumet under the auspices of the Belgian Red Cross in conjunction with the local institution of the National Child Welfare Society, allowed us to obtain most valuable data which seemed to answer to the desiderata fixed by eugenic method.

We have chosen amongst the groups of infants those babies whose mother or father is tubercular but living under healthy conditions.

In every case, the diagnosis of tuberculosis has been established by a physician and the normal character of the environment noted by a visiting nurse knowing all the families for at least a year, and enjoying their confidence. After enquiry she reported on: the quarter inhabited and its healthiness, the hygiene of the house and any possibility of contagion, the feeding, the cleanliness of the parents, the economic conditions of the family and the neighbourhood.

We have further been able to use the curve growths obtained by the staff of the Child Welfare Institute at Jumet.

An infant's vitality can not be assessed by quantitative assessments. It would be impossible to take anthropometric measurements at the moment of birth, and any indications which can be deduced would have only the most doubtful value.

Neither can one base anything on the actual birth weight. At this moment of life the infant's weight is highly variable (removal of meconium, loss of water, length and nature of labour). On the other hand, the weight of the infant is influenced by feeding and varies with the tiniest ailment even from hour to hour.

The curve of growth, on the contrary, may be much more useful. It expresses the increase in weight of the infant and makes it possible to judge of this increase in comparison with a normal curve. Further, it shows the first individual reactions to life, reactions which themselves are indications of vitality.

At birth the infant is nothing but a digestive tract, it is this delicate apparatus which requires several months for adaptation.

On comparing the development of different normal groups one can see that Curves can be shown of weights differing somewhat from each other, nevertheless a general increase remains comparable throughout and one can be super-imposed upon another.

In order to eliminate other disturbing factors in the distribution of cases we have only recorded the weight from the first month onwards, taking children who were breast fed, and we have excluded primiparous and gemelliparous infants.

We have thus been able to form a group as homogeneous as possible, taking the risk of losing in quantity what we have gained in precision. We shall furthermore beware of drawing general conclusions.

We regard this enquiry as a preliminary work showing only the scope and the plan of the phenomena to be observed.

C.—Results.

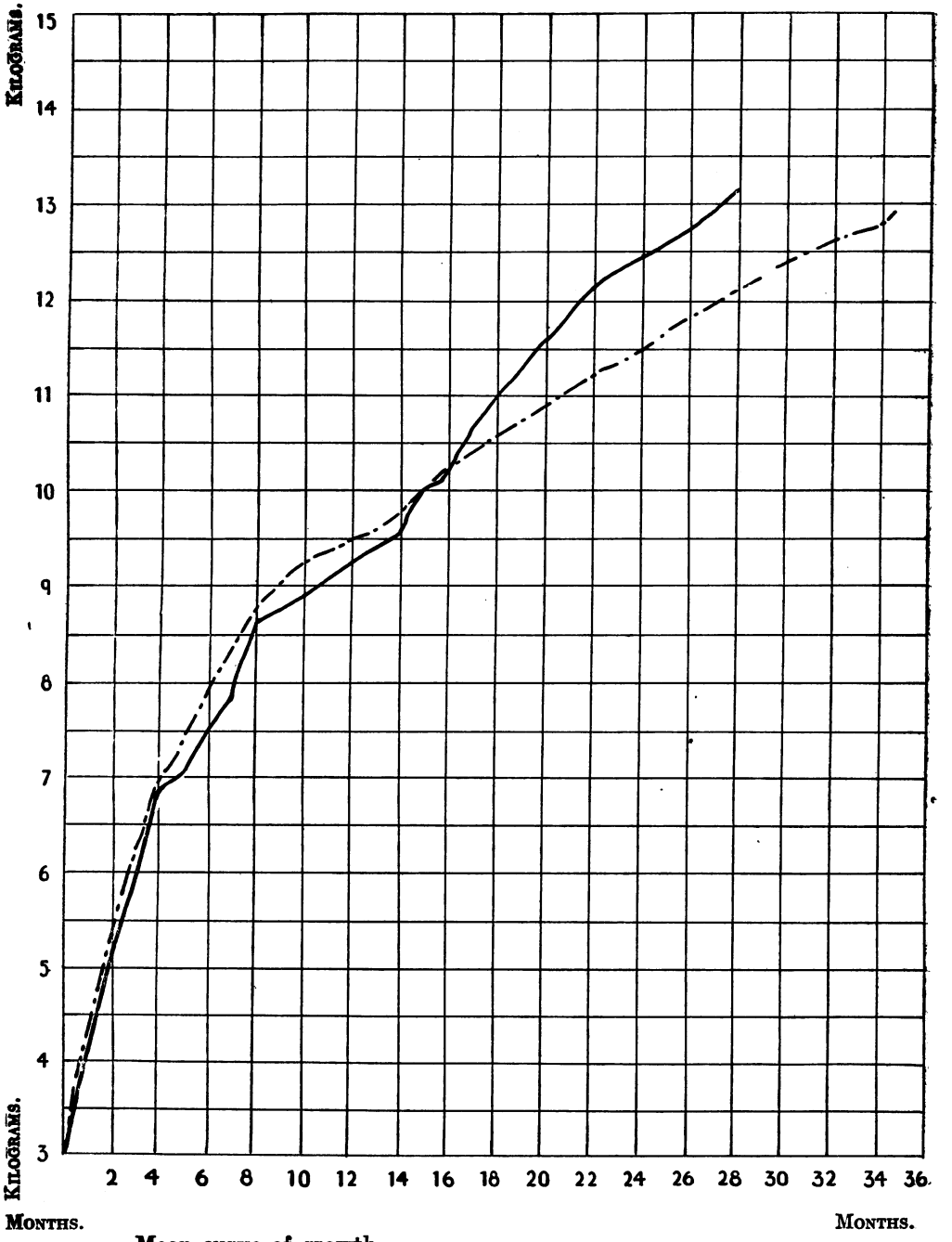
Comparison makes judgment possible; for this operation implies two elements, one fixed constant, making the criterion for comparison; such a datum is given in the present case by the normal curve of growth.

The National Institute for Child Welfare has produced a curve which is called normal, representing the mean of curves from a great number of childrem. These have been obtained from an examination of infants which has been going on for twenty years; children fed by their mothers or on pure milk, which have shown all the marks of perfect health and normal physiological constitution.

It seems unnecessary to discuss the general value of this curve, but it seemed indispensable to our purpose to obtain a mean curve of development of the normal children belonging to the environment from which the material for this enquiry is drawn.

In this case the curves were taken of the growth of a hundred children, taken at random, living in a wholesome environment. The number of cases, of course, is not sufficiently large to be regarded as representative and comparable with that which has been drawn up by the Institute of Public Welfare, but as it is only needed for comparison with the small number of cases here presented, it can be accepted as a sample.

It gives moreover, the advantage of working on the same scale and with homogeneous groups.



Mean curve of growth.

(a) de l'Oeuvre Nationale de l'Enfance. — - — - — - — -

(b) a Hundred Children of the Commune of Jumet. ————

Comparing the two curves given herewith, it will be seen that they are super-imposed from birth up to the age of four months. Between this latter age and sixteen months the two curves are always parallel, above that age however one greatly surpasses the other.

These differences may be due to several causes; difference in the number of children observed, influence of the industrial centre, feeding, etc.

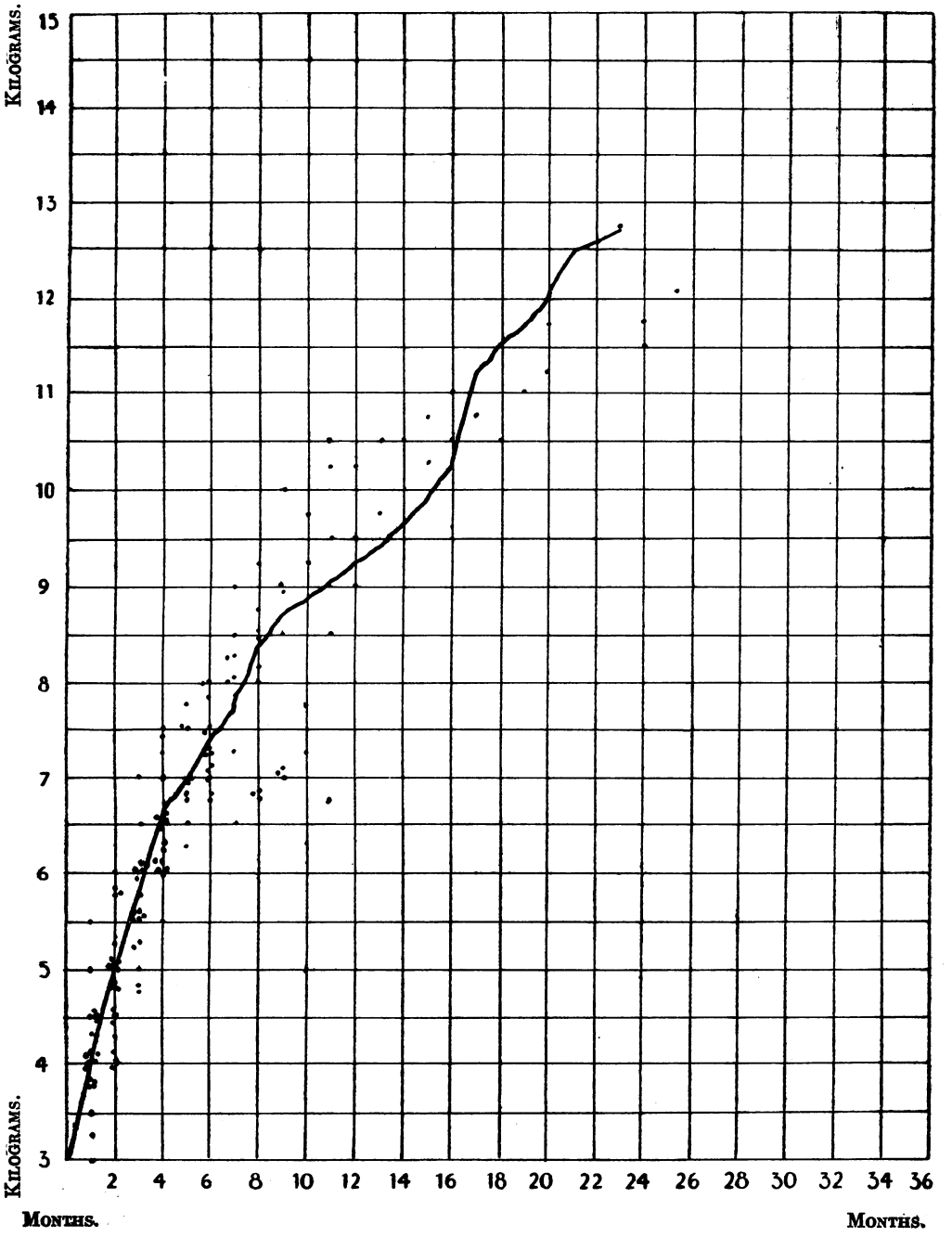
It would be interesting to go deeply into this question and to analyse the disparity between these curves by taking measurements under identical conditions. These differences noted show the need of taking into account the influence of environment when it comes to analysing the biological elements of the vitality of a given population.

It must also be noted that in order to obtain critical precision, the standard deviation for the values of this curve should be ascertained. A weight, although above or below the average, may be within the limits of normal variability, which is fixed by an estimate based on probability. It would be desirable in future to bear this fact in mind when it may be desired to obtain a standard growth curve for the children of our country.

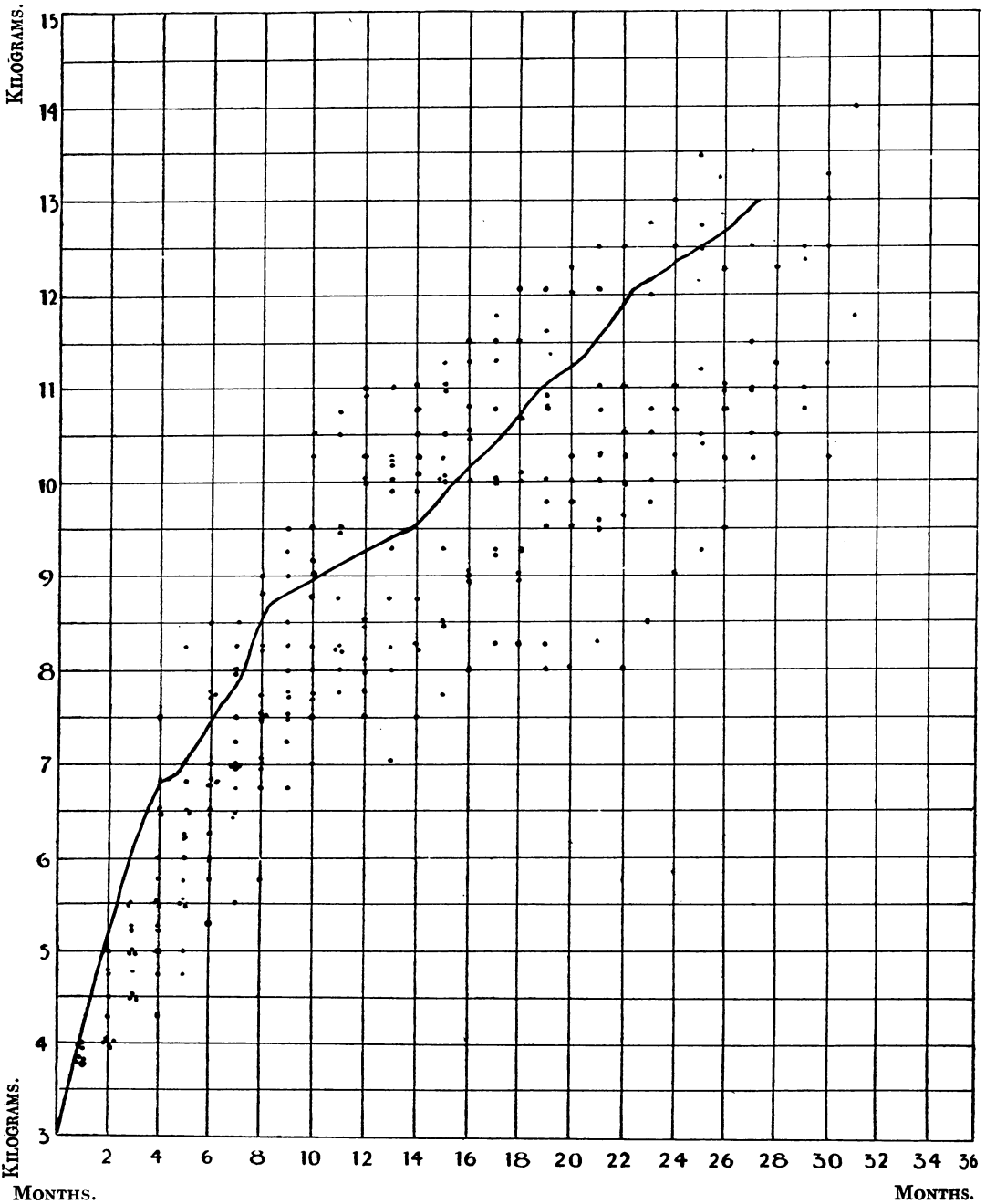
For want of numbers, it is not possible to establish the mean weight of children, offspring of tubercular parents; and it is only possible to analyse the difference in weight of these children by comparing it with the mean curve of healthy chidlren.

As control, we take by the same method the dispersion of weight; (1) of an equal number of healthy children, born of healthy parents, living in healthy environment and taken at random; (2) of healthy children, born of healthy parents, but living in unhealthy surroundings.

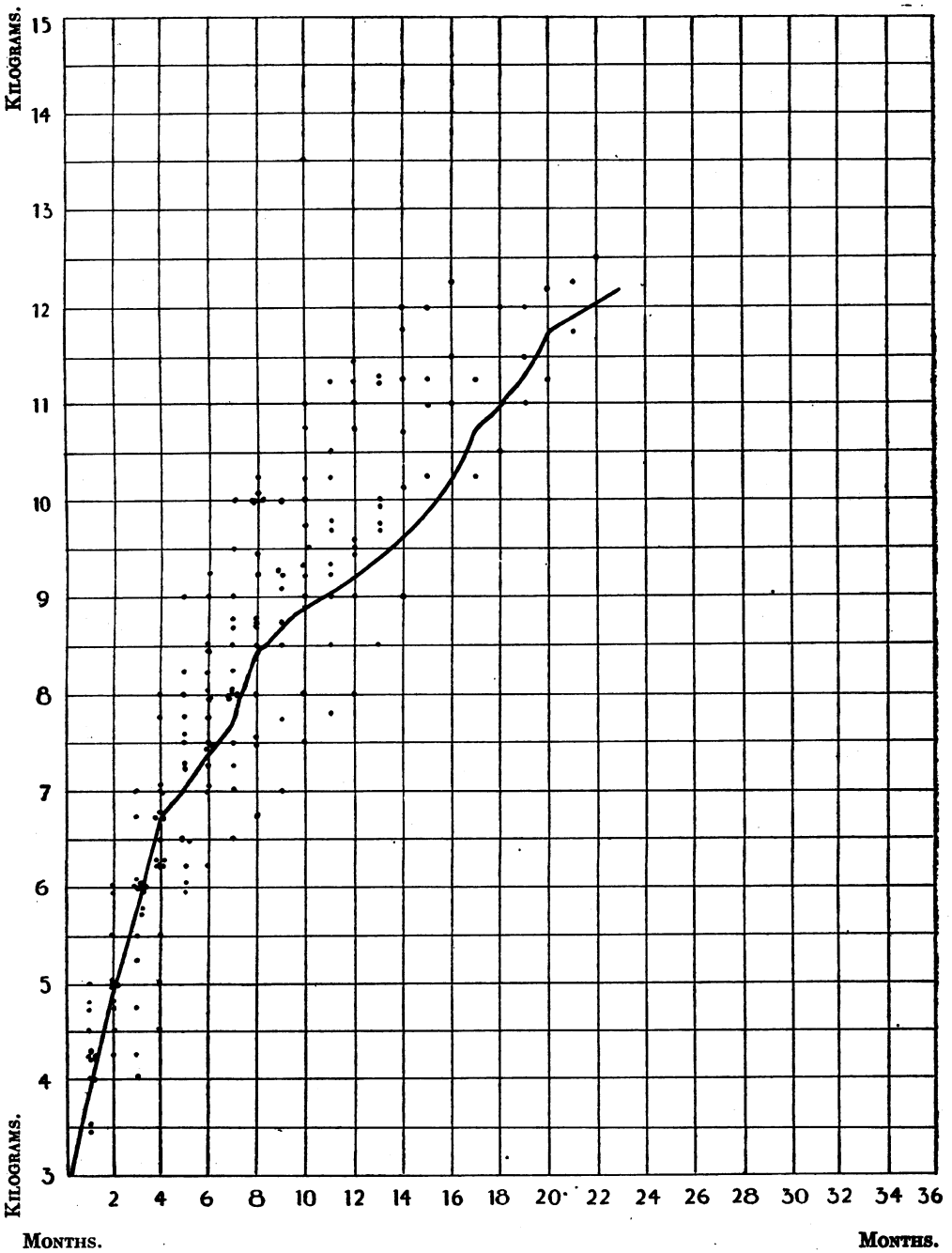
Here are shown these three curves from which it is possible to deduce the following facts:



Mean curve of growth of healthy children offspring of healthy parents living in an unfavourable environment, 21 cases.



Mean curve of growth of children offspring of tubercular parents, 21 cases.



Mean curve of growth of healthy children offspring of healthy parents living in favourable environment.

In the offspring of healthy parents, the curve of growth is parallel to the standard curve and moreover, at about six months old the majority of children are above this curve, and the mode of dispersion approaches the diagonal.

In the offspring of healthy parents living in unfavourable environment, the scatter of weights is narrower and is massed round the normal curve. Very few children are above this curve. A great number tend to remain below, but not much below the curve.

In the offspring of tuberculous parents, the majority of weights fall below the normal, scatter spreads below this curve, few cases rise above it, and, from birth to six months, all the weights are below the mean. Growth is irregular and slow; it departs from the normal. It seems that the organism has more difficulty in adapting itself and uses its power of growth inperfectly.

The same contrasts may be observed in the number of illnesses contracted during the first year of life.

*Out of 21 cases observed, (1) of the offspring of healthy parents living in a healthy environment, 8 have contracted illnesses; (2) offspring of healthy parents living in an unhealthy environment, 9 have contracted illnesses; (3) offspring of tuberculous parents: of these children 23 cases of illness have occurred, or 104%, that is to say, that some children have been ill twice during that period.

These deviations can only be accounted for by the difference in adaptability and individual resistance of the infants.

As the *mesological* influences were identical and constant, it would seem that these differences in vitality are due to hereditary influences. This involves the transmission of a less resistant physiological reaction and doubtless greater susceptibility to tuberculosis.

Such are the facts which seem to stand out in this preliminary examination.

A more intense statistical study would be necessary to verify these facts, and it is to be hoped that our Institutions of Social Hygiene will undertake it.

D.—Interpretation of Results.

In the re-action of the individual to the influences of environment, it has yet to be discovered in what measure this observation corresponds to facts established by experiment.

First may be noticed the work undertaken in the United States by S. Wright†. Working on 23 pairs of guinea-pigs of pure breed, he cross-bred brothers and sisters for 45 generations. From this inbreeding a more or less heterogeneous descent resulted. New combinations of hereditary characteristics appeared and were fixed. It was by this means that Wright secured five lines of guinea-pigs particularly resistant to inoculations of Koch's bacillus. He was able to obtain a regular scale of variation in tubercular resistance by crossing the offspring among themselves and with other stocks, and the resistance factor acted as a Mendelian dominant.

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* Each group includes 21 cases.

† Sewall Wright: "The effects of inbreeding and crossbreeding pigs." U.S.A. Department of Agriculture: Washington. 1922.

The union of progeny of the same descent, having identical hereditary potential, only produced new characters by new combinations of these characters. Different phenotypes have been obtained from the same genotypes.

All recessive characters were brought to light and resulted in a veritable exhaustion of the possible combinations in the hereditary material.

The guinea-pig race, which was used as a starting point, contained in itself certain factors or certain tendencies favouring resistance to tuberculosis. Had nature worked alone these charactersistics might have appeared sooner or later, more or less modified within the limits fixed by the hazard of fertilization.

These experiments seem to show that the degree of resistance of the guinea-pig race observed was determined by the genetic composition of the animal itself.

The same phenomena have been observed for other elements of vitality such as weight, curve of growth and longevity.

Side by side with these studies, which simply tend to prove hereditary transmission of resistance to tuberculosis, others exist which throw a clear light on the mechanism of this resistance.

According to Professor Dustin, *in order that a nucleus may divide, it is necessary that the organism should supply it with a certain quantity of nuclear protein regulated by the thymus. Dr. Dustin further shows that variation in the division of the nucleus depends on the nature of the cytoplasm which is accompanied by physico-chemical reaction (cellular permeability).

The cell responds to the interplay of cynases by division, by the interplay of pycnases the first process can be regulated by reducing the number of cell divisions.

Carrel's investigations show the importance of the embryonic medium; this furthers the growth of tissues and assures their partial permanence, whilst other media only permit of a temporary survival.†

In the first instance, the cells are utilising intrinsic energy while in the second they are dependent on residual energy.

These two types of energy of growth are the resultants of different factors; the age of the animal, the presence of inhibitory or activating substances, or of trephones. The inter-action of these two groups of factros gives the nature of the medium which activates or retards growth.

Growth dynamics thus appear to be a function of the environmental medium and the cellular activity.

These researches have yet to be confirmed and completed; but they enable us to conceive of the facts as here described.

They show also that the problem of heredity in tuberculosis is as

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* A. P. Dustin—

Archives of Biology. t.XXX. 1920.
Accounts of the Biological Society, 1920—23.
Annals and Bulletin of the Brussels' Royal Society of Medical and Natural Sciences.

† See also Strangeways. (*Note.*)

yet far from solution, and that from the collaboration of all engaged in research, may one day spring a new inspiration which will necessarily influence social activity against this great scourge.

E.—Conclusion.

The comparison between the curves of growth of offspring of tuberculous parents and those of healthy parents, shows that the former are born with a reduced coefficient of vitality as compared with the latter.

Their power of growth and their resistance appear to be less. All things being equal and constant as regards the environment, these differences seem to have an hereditary origin.

These observations agree with recent discoveries in general biology and genetics, but are necessarily provisional in character. It would be desirable that a similar, but more extensive enquiry should be undertaken by our Societies of Social Hygiene.